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Statistical Power to Detect Genetic Loci Affecting Environmental Sensitivity

Peter M. Visscher · Danielle Posthuma

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Abstract There is evidence in different species of genetic control of environmental variation, independent of scale effects. The statistical power to detect genetic control of environmental or phenotypic variability for a quantitative trait was investigated analytically using a monozygotic (MZ) twin difference design and a design using unrelated individuals. The model assumed multiplicative or additive effects of alleles on trait variance at a bi-allelic locus and an additive (regression) model for statistical analysis. If genetic control acts on phenotypic variance then the design using unrelated individuals is more efficient but 10,000s of observations are needed to detect loci explaining at most 3.5% of the variance of the variance at genome-wide significance. If genetic control acts purely on environmental variation then an MZ twin difference design is more efficient when the MZ trait correlation is larger than ~ 0.3 . For a locus that explains a given proportion of the variation in variance, twice the number of observations is needed for detection when compared to a locus that explains the same proportion of variation in phenotypes.

Keywords Environmental sensitivity · $G \times E$ interaction · Genetic association · Statistical power

Introduction

Genotypes can have different phenotypic values in different environments. The difference in phenotypic values of a genotype across environments is termed the environmental sensitivity or reaction norm (Falconer 1990; Jinks and Connolly 1973; Lynch and Walsh 1998). Environmental sensitivity does not necessarily imply a genotype by environment interaction in the sense that the rank of genotypes changes across environments. For example, phenotypic values can be more variable in one environment than another without changing the ranks of genotypes across environments, in which case the genetic correlation of phenotypic measurements across environments is unity. Ignoring this kind of heterogeneity of variance will induce a ‘pseudo-interaction’ (Dickerson 1962) in an analysis of variance which would disappear when adjusting for heterogeneity of variance across environments, for example by a suitable scale transformation. For plant and animal breeders, the distinction between interactions due to heterogeneous variances and genetic correlations less than unity matters when artificial selection programmes aim to maximise response to selection across environments. In human genetics (and in ecological genetics), this distinction is less important, and heterogeneity of variance across environments on the observed scale may be of interest. For example, estimates of heritability for intelligence (IQ) have been shown to vary across socio-economic groups (Turkheimer et al. 2003), the heritability of alcohol consumption is reported to vary as a function of marital status (greater heritability in single versus married individuals

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P. M. Visscher (✉)
Queensland Institute of Medical Research, 300 Herston Road,
Herston 4006, Australia
e-mail: peter.visscher@qimr.edu.au

D. Posthuma
Section Medical Genomics, VUMC, Amsterdam,
The Netherlands

D. Posthuma
Center for Neurogenomics and Cognitive Research,
section Functional Genomics, Vrije Universiteit,
Amsterdam, The Netherlands

(Heath et al. 1989), and heritability of age at first sexual intercourse changes as a function of historical cohort (greater heritability in more recent cohorts (Dunne et al. 1997). Given that these traits are thought to be highly polygenic, changes in heritability across different environmental levels are unlikely to be due to the interaction effect of the environment with one single genotype. Rather, it seems likely that the environment interacts with multiple genetic loci that share a similar function and may therefore also share similar environmental sensitivity.

Environmental sensitivity does not necessarily imply a response to external micro-environments, but could also be due to intrinsic factors, for example those related to developmental stability/noise. Waddington's concept of canalisation invokes a buffering of the phenotype against perturbations and hence reduced variance (Gibson and Wagner 2000). Phenotypic plasticity is the capacity of genotypes to change phenotype in a response to a change in environmental conditions (De Jong and Bijma 2002). Variation in phenotypic plasticity between genotypes would result in heterogeneity of phenotypic variance between genotypes.

Theoretical models have been proposed to explain the evolution of phenotypic variance (Bull 1987; Slatkin and Lande 1976; Zhang and Hill 2005; Zhang and Hill 2007; Zhang and Hill 2008) but these are not consistent with the magnitude of variance components observed in populations. In particular, theoretical models generally predict lower heterogeneity of variance than is observed. There is evidence of genetic control of environmental and phenotypic variation within single environments in a range of species, including *Drosophila* (Mackay and Lyman 2005), pigs (Sorensen and Waagepetersen 2003), snails (Ros et al. 2004), maize (Ordas et al. 2008) and chickens (Wolc et al. 2009). Estimating or detecting genetic variation in environmental or phenotypic variance is difficult because variances are inherently more variable than means. In experimental organisms large sample sizes can be constructed for specific genotypes, and the relationship between genotype and environmental variance can be estimated (Mackay and Lyman 2005; Ordas et al. 2008). The efficiency of designs to estimate variances in heterogeneity of variance was quantified by Hill (Hill 2004).

In outbred populations of livestock, residual variances (i.e., variances of effects unique to individuals) from linear models on mean effects have been modelled to estimate genetic effects on these variances. Typically, linear models of the logarithm of the estimated residual variances are used to estimate genetic variance of residual variation (Ros et al. 2004; Sorensen and Waagepetersen 2003; Wolc et al. 2009). For example, a heritability of 0.02–0.04 was estimated for residual variation of body weight in broiler chickens (Wolc et al. 2009).

In human populations, the squared difference in trait values between monozygotic (MZ) twins (i.e. their phenotypic discordance) provides a direct measure of the within-pair variance, and can therefore be used to investigate environmental sensitivity (Martin et al. 1983). For some behavioral traits in human populations, there is evidence of heterogeneity of variance. For example, Benyamin et al. (2006) reported a leptokurtic distribution of MZ pair differences for childhood IQ, consistent with heterogeneity of variance.

In the population, the relationship between a genotype (e.g. a SNP genotype) and environmental variance can be investigated in the absence of pedigree information by calculating the variance for each genotype and performing a statistical test on the estimated variances. For example, Martin and colleagues reported heterogeneity of environmental variance in alpha-1-antitrypsin as a function of genotype at the protease-inhibitor locus (Martin et al. 1987). Large samples are available for such analyses following the recent genome-wide association study revolution. The MZ difference design is particularly appealing because systematic effects on the phenotypes are eliminated when taking the (squared) difference. When using the MZ difference design, Wray and co-workers did not find any evidence for heterogeneity of within MZ pair variance for depression when pairs were stratified according to their genotype at the serotonin receptor gene (Wray et al. 2008), suggesting no gene by environment interaction for this gene in the context of depression.

In this study we quantify the power to detect genetic loci that affect either environmental or phenotypic variability in designs using either unrelated individuals or pairs of monozygotic twin (MZ) pairs.

Methods

Assumptions and notation

A single SNP with alleles A and B is in Hardy–Weinberg equilibrium, with p the frequency of allele B. We assume that the SNP has an effect on the trait variance but no effect on the trait mean. With empirical data, a suitable transformation, for example a log transformation, may have to be applied to ensure no mean–variance relationships. We assume a normally distributed quantitative trait with phenotypic variance of unity for genotype AA. A proportion $(1 - r_{MZ})$ of this variance is due to environmental factors, with r_{MZ} the phenotypic correlation between MZ twin pairs. We consider a number of scenarios:

1. The effect of the SNP is on the phenotypic variance or on the non-shared environmental variance only.
2. Effect of the SNP on the variance is either multiplicative or additive.

3. Phenotypic measurements are available from N unrelated individuals in the population or on N_{MZ} monozygotic twin pairs.

In each scenario we test for heterogeneity of variances as a function of genotype. Note that in the absence of heterogeneous variances, $E(y - \mu)^2 = \sigma^2$, $E(y - \mu)^4 = 3\sigma^4$ and $\text{var}(y - \mu)^2 = 2\sigma^4$, hence values of 1, 3 and 2, respectively, when $\sigma^2 = 1$.

We assume that statistical analysis is performed by a linear regression of $(y - \mu)^2$ on genotype indicator scores 0, 1 and 2, corresponding to genotypes AA, AB and BB, similar to the Haseman–Elston regression of within-family variance on the proportion of alleles shared identical by descent (Haseman and Elston 1972).

Heterogeneity of phenotypic variance

Under an additive model the difference in variance between different genotypes is quantified as a fixed effect that is added to the variance as a function of genotype indicator. In a multiplicative model the difference in variances between genotypes is quantified by multiplying the variance with λ as a function of genotype indicator. We derive the results for a multiplicative model. Derivations for an additive model are in the Appendix. For small effects of the SNP alleles on the variance the multiplicative and additive model are similar.

The model is summarised in Table 1. Phenotypic variances ($= E(y - \mu)^2$) of the three genotypes are λ^x , with $x = 0, 1, 2$. Expectations of the fourth moments are $3\lambda^{2x}$.

In the population, the phenotypic variance is $E_x(\lambda^x) = (1 + p(\lambda - 1))^2$ (Wray et al. 2007). This expression was derived from the Hardy–Weinberg genotype frequencies: $E_x(\lambda^x) = (1 - p)^2\lambda^0 + 2p(1 - p)\lambda^1 + p^2\lambda^2 = [(1 - p) + p\lambda]^2 = (1 + p(\lambda - 1))^2$. The expectation of the fourth moment is $3(1 + p(\lambda^2 - 1))^2$. Hence, the variance of $(y - \mu)^2$ in the population is

$$\text{var}(y - \mu)^2 = 3(1 + p(\lambda^2 - 1))^2 - (1 + p(\lambda - 1))^4.$$

For values of λ close to 1, i.e. when there is little heterogeneity of variance across genotypes), this approximates to $2(1 + 4p(\lambda - 1))$. The covariance of x and $(y - \mu)^2$ is $2p(1 - p)(\lambda - 1)(1 + p(\lambda - 1))$, and the variance of x is $2p(1 - p) = h$. Therefore, the proportion of variation in

$(y - \mu)^2$ that is explained by the SNP is, after some algebra,

$$R^2 = \left[\text{cov}((y - \mu)^2, x) \right]^2 / \left[\text{var}(x) \text{var}((y - \mu)^2) \right] \\ = h(\lambda - 1)^2 [(1 + p(\lambda - 1))]^2 \\ / \left[3(1 + p(\lambda^2 - 1))^2 - (1 + p(\lambda - 1))^4 \right],$$

or, approximately,

$$R^2 \approx \frac{1}{2}h(\lambda - 1)^2 [(1 - 2p(\lambda - 1))] \approx \frac{1}{2}h(\lambda - 1)^2$$

The approximation is good when λ is close to 1 and/or p is small. For $p = \frac{1}{2}$, the approximation error, calculated from the ratio $R^2(\text{approximation})/R^2(\text{exact})$, is 11, 24 and 75% for λ values of 1.1, 1.2 and 1.5, respectively. When $p = 0.10$, the errors are 2, 5 and 17%, respectively. The expression for the approximation of R^2 is half of that for the proportion of variation explained by a SNP with an additive effect of $(\lambda - 1)$ standard deviations. This conclusion is not surprising because in general the sampling error of a mean is σ^2/N and that of a variance is $2\sigma^4/N$.

The non-centrality-parameter (NCP) of a Chi-square test for association is NR^2 , so approximately $\frac{1}{2}Nh(\lambda - 1)^2$.

Heterogeneity of environmental variance

We define λ_E as the multiplicative effect on the environmental variance. The ‘environment’ here is that which is unique to each individual; the environment shared between family members is not considered here. The expected values of the second and fourth moments are,

$$E(y - \mu)^2 = r_{AA} + (1 - r_{AA})\lambda_E^x \text{ and}$$

$$E(y - \mu)^4 = 3[r_{AA} + (1 - r_{AA})\lambda_E]^2,$$

with $(1 - r_{AA})$ defined as the proportion of phenotypic variance due to environmental effects among AA genotypes. r_{AA} is also the MZ twin correlation of pairs with genotype AA.

The variance in the population is

$$E_x[r_{AA} + (1 - r_{AA})\lambda_E^x] \\ = r_{AA} + (1 - r_{AA})[1 + p(\lambda_E - 1)]^2,$$

and the MZ twin correlation in the population is,

$$r_{MZ} = r_{AA} / \left(r_{AA} + (1 - r_{AA})[1 + p(\lambda_E - 1)]^2 \right).$$

When $p(\lambda_E - 1)$ is small the MZ correlation in the population is similar to the MZ correlation in each of the three genotype groups.

No simple expression of $\text{var}(y - \mu)^2 = E_x(y - \mu)^4 - E_x(y - \mu)^2$ was found, but a good approximation is,

Table 1 Multiplicative model for phenotypic variances

Genotype	Frequency	Genotype indicator (x)	$E(y - \mu)^2$	$E(y - \mu)^4$
AA	$(1 - p)^2$	0	1	3
AB	$2p(1 - p) = h$	1	λ	$3\lambda^2$
BB	p^2	2	λ^2	$3\lambda^4$

$$\text{var}(y - \mu)^2 \approx 2[1 + 2p(\lambda_E - 1)(1 - r_{AA})]^2$$

The covariance between x and $(y - \mu)^2$ is $h(\lambda_E - 1)(1 - r_{AA})(1 + p(\lambda_E - 1))$, and an approximation of the regression R^2 ,

$$R^2 \approx \frac{1}{2}h(\lambda_E - 1)^2(1 - r_{AA})^2$$

Hence, relative to the case of heterogeneity of phenotypic variance, the association signal between a SNP and phenotypic variance is reduced by a factor of $(1 - r_{AA})^2$ when only environmental variances are heterogeneous.

Monozygotic twins

The squared difference between trait values of monozygotic twin pairs is a direct estimate of twice the variance of environmental effects that are unique to each individual. Whether variances are heterogeneous phenotypically or environmentally, the expectation of the proportion of variance explained by the SNP from a regression of the MZ squared difference on allelic dose (x) is the same. The NCP for MZ twin pairs is therefore,

$$\text{NCP}_{\text{MZ}} = N_{\text{MZ}}R^2 \approx \frac{1}{2}N_{\text{MZ}}h(\lambda - 1)^2$$

Results

In Fig. 1 we give the required sample size to detect differences in phenotypic variance that are associated with a SNP for a GWAS (type-I error rate of 10^{-6}), as a function of a multiplicative effect on the variance varying from 1.05 to 1.5. This range of effect sizes imply that the SNP explains 0.06% ($\lambda = 1.05$), 0.2% ($\lambda = 1.1$) to 3.5% ($\lambda = 1.5$) of the variance heterogeneity in the population. SNPs that are associated with mean effects typically explain less than 1% of the trait variation. Figure 1 shows

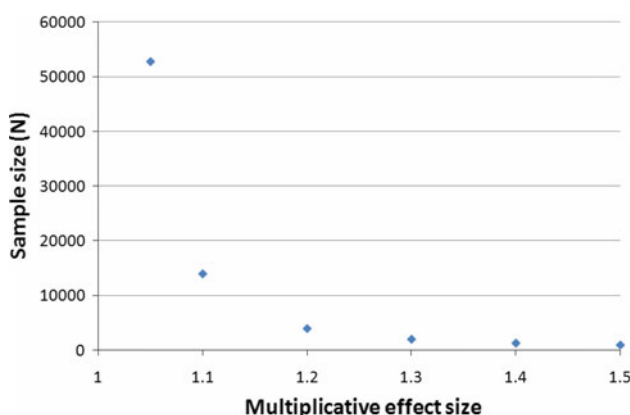


Fig. 1 Sample size (either N unrelated individuals or N MZ twin pairs) to detect heterogeneous variance when SNP acts on entire phenotype. $p = \frac{1}{2}$, type-I error rate = 10^{-6} , power = 80%

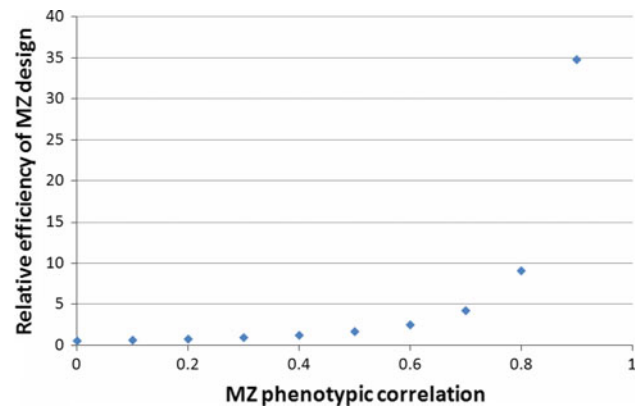


Fig. 2 NCP per phenotyped individual of an MZ design relative to a design with unrelated individuals, when $\lambda_E = 1.2$ and $p = \frac{1}{2}$

that very large sample sizes are needed to detect heterogeneous variances.

In Fig. 2, the relative efficiency per phenotyped individual is shown for the MZ design and the design of unrelated individuals, when heterogeneity acts on environmental variation only ($\lambda_E = 1.5$, $p = 0.5$). This would be an example of environmental sensitivity under genetic control. For MZ correlations > 0.3 , which are frequently observed with real data, the MZ design is more efficient than the design based upon unrelated individuals.

Given the assumptions made, the same statistical power is obtained from N unrelated individuals as N_{MZ} pairs when the SNP acts on phenotypic variance, even though in the latter case there are $2N_{\text{MZ}}$ phenotypes. The reason is that for the MZ twin pairs, only the information contained in the trait difference is used and the information contained in the trait sum is ignored.

However, if the SNP acts on the environmental variance only, then MZ twin pairs provide a better estimate of the environmental variance, and statistical power using N_{MZ} pairs is more powerful than using N unrelated individuals. Equivalent power is obtained when $N_{\text{MZ}} = N(1 - r_{AA})^2$. For a constant number of phenotypes ($2N_{\text{MZ}} = N$), the same power is obtained with MZ pairs as unrelated individuals if $r_{AA} = 1 - \sqrt{\frac{1}{2}} \approx 0.29$. For larger MZ phenotypic correlations, the MZ difference design is more powerful.

Discussion

The power to detect genetic loci that affect either environmental or phenotypic variability in designs using either unrelated individuals or pairs of monozygotic twin (MZ) pairs was investigated. It was shown that very large sample sizes are needed to detect heterogeneous variances. For the

best scenario ($\lambda = 1.5$, $p = 0.5$), the locus explained 3.5% of the variance, which is large when compared to the effect sizes of SNPs on mean phenotypes from genome-wide association studies.

In addition, it was shown that if a locus acts on the phenotypic variance, a design that includes N unrelated individuals is as powerful for the detection of environmental sensitivity as a design that includes N_{MZ} pairs. As the latter contains $2N_{\text{MZ}}$ phenotypes, it is twice as costly in terms of phenotypic data collection, and therefore the unrelated individuals' design will be preferred. If, however, the genetic locus acts solely on the environmental variance and the MZ correlation is >0.3 , the MZ design is more powerful than the design based upon unrelated individuals.

Studies in evolutionary biology and genetic studies in crops and animals have shown that environmental sensitivity is extremely common (Lynch and Walsh 1998). Eaves and colleagues (Eaves et al. 1977) stated that in experimental organisms rarely more than 20% of variance between treatments and genotypes is attributable to G \times E, but it remains to be tested how much of the variance in human traits can be ascribed to environmental sensitivity of genetic loci.

Can we distinguish between heterogeneity of phenotypic and environmental variance using empirical data? In principle this is possible because heterogeneity of environmental variance can be estimated using an MZ design and this amount of heterogeneity would predict the magnitude of phenotypic variance heterogeneity, a prediction that can be tested empirically using the design of unrelated individuals.

The comparison made between the population and MZ designs assumes that measurements on unrelated individuals can be adjusted for systematic effects, such as sex, age, cohort etc. and also that there is no association between genotype and such effects. If systematic effects remain then they will cause the variance of each genotype to increase, thereby reducing power to detect effects of individual loci on variation. The MZ design does not suffer from this because most if not all systematic differences disappear when the difference between the MZ phenotypes is used for analysis.

Finally, we note that the statistical analysis we have used in this study for unrelated individuals is straightforward to implement in a GWAS or a meta-analysis of several GWAS. All one needs to do is to replace an observation y on an individual with the square of its standardised residual, i.e. adjusting observations for fixed effects and covariates and for the phenotypic standard deviation of the sample and then squaring them. If the only fixed effect is an overall mean then the mean centred and standardised value to use for analysis is simply $[(y - \mu)/\sigma]^2$. Since most GWAS and in particular meta-analyses already work with residual values,

Table 2 Additive model for phenotypic variances

Genotype	Frequency	Genotype indicator	$E(y - \mu)^2$	$E(y - \mu)^4$
AA	$(1 - p)^2$	0	1	3
AB	$2p(1 - p) = h$	1	$1 + \delta$	$3(1 + \delta)^2$
BB	p^2	2	$1 + 2\delta$	$3(1 + 2\delta)^2$

a simple squaring of these values would allow an immediate GWAS on phenotypic variation.

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Appendix: Additive model

The model is summarised in Table 2. Phenotypic variances ($= E(y - \mu)^2$) of the 3 genotypes are $(1 + x\delta)$, with $x = 0, 1, 2$. Expectations of the fourth moments are $3(1 + x\delta)^2$.

The phenotypic variance in the population is $1 + 2p\delta$ and the covariance between x and $(y - \mu)^2$ is $h\delta$. The variance of $(y - \mu)^2$ is,

$$\text{var}(y - \mu)^2 = 2[1 + 4p\delta + p\delta^2(3 + p)] \approx 2[1 + 4p\delta],$$

when δ is small. The regression R^2 is therefore,

$$R^2 = \frac{1}{2}h\delta^2 / [1 + 4p\delta + p\delta^2(3 + p)] \approx \frac{1}{2}h\delta^2[1 - 4p\delta] \approx \frac{1}{2}h\delta^2.$$

As expected, the additive and multiplicative model are similar when δ is small because $1 + 2\delta \approx (1 + \delta)^2 = \lambda^2$.

See Table 2.

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